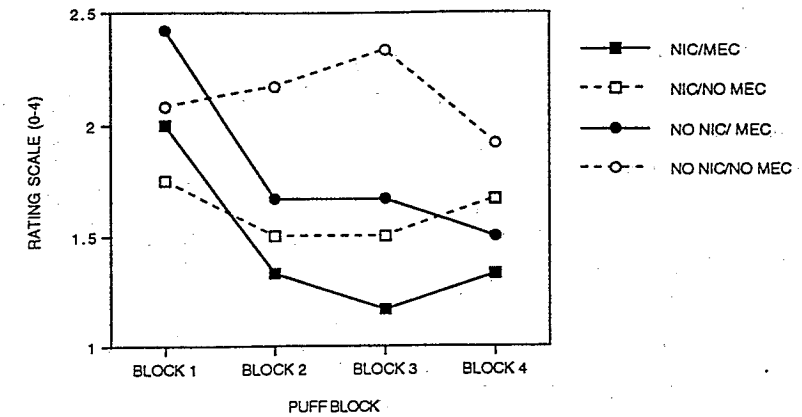
Combined Administration of Agonist-Antagonist as a Method of Regulating Receptor Activation

JED E. ROSE,[a,b] EDWARD D. LEVIN,[b]
FREDERIQUE M. BEHM,[b] ERIC C. WESTMAN,[a,c]
ROY M. STEIN,[a,b] JAMES D. LANE,[b] AND GAIL V. RIPKA[b]

[a]*VA Medical Center*
Durham, North Carolina 27705

Departments of Psychiatry[b] and Medicine[c]
Duke University
Durham, North Carolina

Co-administration of an agonist with an antagonist may occupy a greater number of receptors than either drug alone, thereby attenuating further response to a phasic stimulus. At the same time, it is hypothesized that the tonic actions of the agonist and antagonist offset one another, regulating receptor activation and avoiding over- or understimulation that would be caused by administration of either agonist or antagonist alone. This hypothesis was tested in the context of drug reward. Twelve smokers rated the rewarding effects of cigarette smoke after separate and combined administration of nicotine and the nicotinic antagonist mecamylamine. Subjects rated test cigarettes after administration of mecamylamine (10 mg) versus placebo capsules, and a nicotine (1.1 mg) versus non-nicotine smoke preload. Smoking withdrawal symptoms, task performance, and cardiovascular activity were also measured. As predicted, mecamylamine significantly attenuated smoking satisfaction, liking, and airway sensations (FIG. 1). The nicotine preload similarly reduced the enjoyable aspects of subsequent test cigarettes, and this action of the preload was *not* prevented by mecamylamine. In contrast, mecamylamine did block nicotine-related increases in heart rate and systolic blood pressure (FIG. 2). Conversely, nicotine counteracted the sedative effects of mecamylamine on tapping speed (FIG. 3) and orthostatic blood pressure response (FIG. 2). Although each drug offset potential side effects of the other, they acted in unison to attenuate smoking satisfaction. Thus, combined agonist-antagonist administration may attenuate drug reward while preventing the withdrawal symptoms or other side effects associated with presentation of agonist alone or antagonist alone. Unlike partial agonists, the current approach of co-administering agonist and antagonist allows for flexible titration of the ratio of agonist-to-antagonist doses.



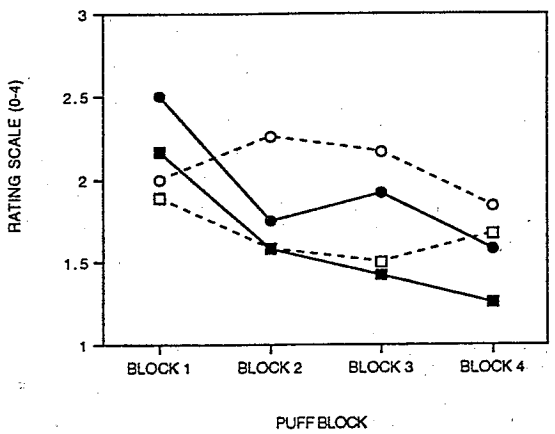


FIGURE 1. Effects of nicotine and mecamylamine on smoking satisfaction (A) and on liking (B) test cigarettes.

[*FIGURES 2 and 3 are on following pages.*]

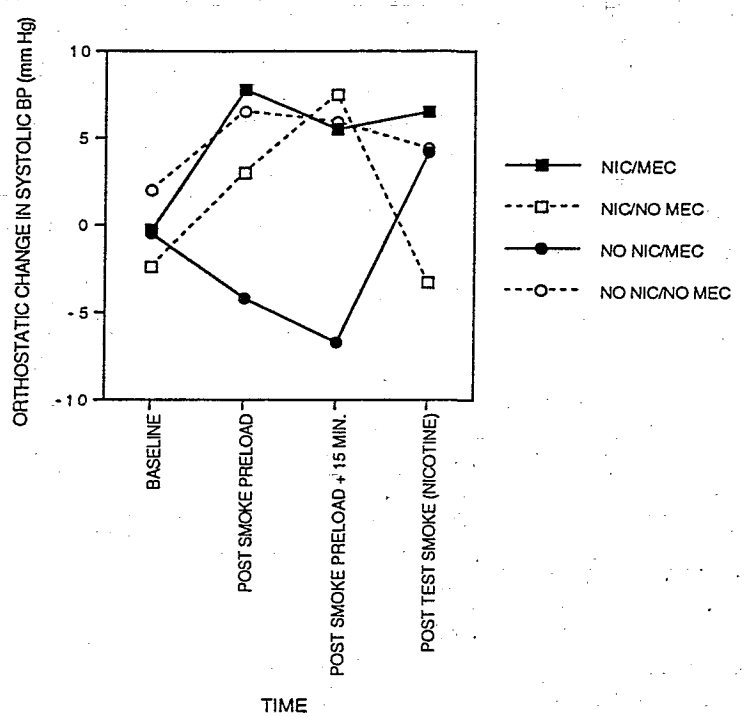


FIGURE 2. Effects of nicotine and mecamylamine on orthostatic response of systolic blood pressure.

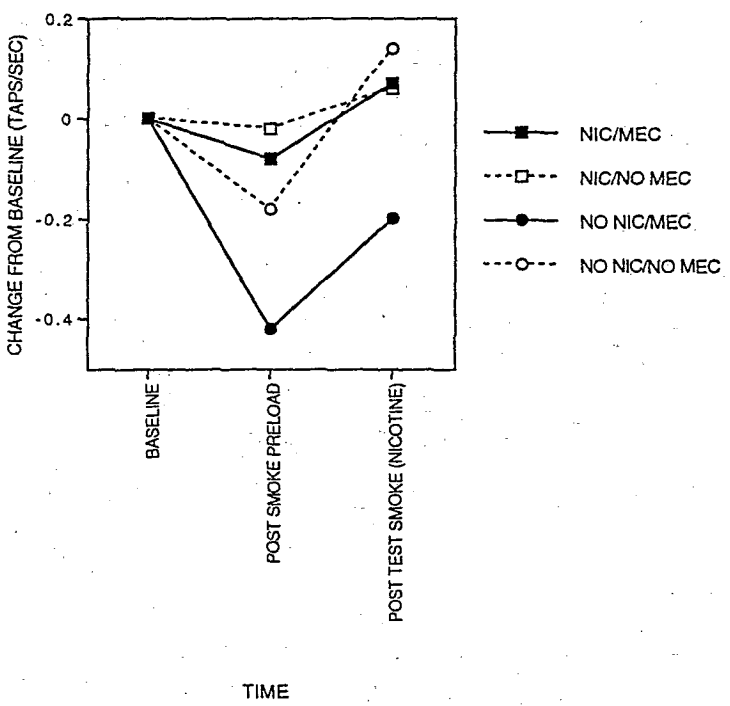


FIGURE 3. Effects of nicotine and mecamylamine on tapping speed.